

Claims

1. Storage stable pharmaceutical formulation comprising at least one pharmaceutically active compound in a diffusion matrix,
5 **characterized in that** the matrix is determined with respect to its essential release characteristics by ethylcellulose or an ethylcellulose-based polymer and at least one fatty alcohol and that the active compounds are released from the substantially non-swellable diffusion matrix in a sustained, invariant and, if several compounds are present, independent manner.
- 10 2. Pharmaceutical formulation according to claim 1,
characterized in that the fatty alcohol comprises lauryl, myristyl, stearyl, cetylstearyl, ceryl and/or cetylalcohol, preferably stearyl alcohol.
- 15 3. Pharmaceutical formulation according to claim 1 or 2,
characterized in that the formulation comprises ethylcellulose.
- 20 4. Pharmaceutical formulation according to one of the preceding claims,
characterized in that the formulation does not comprise relevant amounts of alkaline and/or water-swellable substances, particularly derivatives of acrylic acid and/or hydroxyalkylcelluloses.
- 25 5. Pharmaceutical formulation according to one of the preceding claims,
characterized in that the formulation comprises common pharmaceutical excipients, particularly fillers, lubricants, flowing agents and/or plasticizers.
- 30 6. Pharmaceutical formulation according to claim 5,
characterized in that the fillers are selected from the group comprising sugars, preferably lactose, glucose and/or saccharose, starches and hydrolysates thereof, preferably micro-crystalline cellulose and/or cellactose, sugar alcohols, preferably

REPLACED BY
ART 34 ANDT

sorbitol and/or mannitol, poorly soluble calcium salts, preferably calcium hydrogenphosphate, dicalciumphosphate or tricalciumphosphate and/or povidone.

7. Pharmaceutical formulation according to claim 5,
5 **characterized in that** it comprises magnesium stearate, calcium stearate and/or calcium laureate and/or fatty acids, preferably stearic acid as lubricant.
8. Pharmaceutical formulation according to claim 5,
10 **characterized in that** it comprises highly dispersed silica, preferably Aerosil®, talcum, corn starch, magnesium oxide, magnesium and/or calciumstearate as flowing agent.
9. Pharmaceutical formulation according to claim 5,
15 **characterized in that** it comprises dibutyl sebacate as plasticizer.
10. Pharmaceutical preparation according to one of the preceding claims,
characterized in that the formulation can be stored over a period of at least two years under standard conditions (60% relative humidity, 25°C) in accordance with admission guidelines.
- 20 11. Pharmaceutical preparation according to one of the preceding claims,
characterized in that it comprises opioid analgesics as the pharmaceutically active compounds, preferably morphine, oxycodone, hydromorphone, propoxyphene, nicomorphine, dihydrocodeine, diamorphine, papaveretum, codeine, ethylmorphine,
25 phenylpiperidine and/or derivatives thereof, methadone, dextropropoxyphene, buprenorphine, pentazocin, tilidine, tramadol and hydrocodone and/or opioid antagonists, preferably naltrexone, naloxone, nalmefene, nalorphine, nalbuphin, naloxonazine, methylnaltrexone, ketylcyclazocine, norbinaltorphimine, naltrindol, 6-β-naloxol and/or 6-β-naltrexol.

REPLACED BY
ART 34 AMDT

- 61 -

12. Pharmaceutical formulation according to claim 11,
characterized in that the opioid analgesic and/or the antagonist are present in the
form of their pharmaceutically acceptable and equally active derivatives, such as the
free base, salts and the like, preferably as the hydrochloride, sulfate, bisulfate, ttrate,
5 nitrate, citrate, bittrate, phosphate, malate, maleate, hydrobromide, hydroiodide,
fumarate or succinate.
13. Pharmaceutical formulation according to claim 11 or 12,
characterized in that the formulation comprises at least two active compounds
10 which are oxycodone and naloxone, and wherein oxycodone is present in an amount
ranging from 10 to 150 mg, preferably from 10 to 80 mg and naloxone is present in
an amount ranging from 1 to 50 mg per unit dosage.
14. Pharmaceutical formulation according to claim 13,
15 **characterized in that** it comprises oxycodone and naloxone in a weight ratio
ranging from maximal 25:1, preferably maximal 20:1, 15:1 and more preferably from
5:1, 4:1, 3:1, 2:1 and 1:1.
15. Pharmaceutical formulation according to claim 11 or 12,
20 **characterized in that** it contains oxycodone and naloxone with oxycodone being
present in an amount ranging from 10 to 150 mg, preferably from 10 to 80 mg and
naloxone being present in an amount ranging from 1 to 50 mg.
16. Pharmaceutical preparation according to one of the preceding claims,
25 **characterized in that** the formulation is a tablet, preferably a multi-layered tablet, a
capsule, a dragée, a granulate and/or a powder.
17. Pharmaceutical formulation according to claim 16,
characterized in that the pharmaceutical preparation is suitable for oral, nasal and/or
30 rectal application.

REPLACED BY
ART 34 AMDT

- 62 -

18. Pharmaceutical formulation according to one of the preceding claims, **characterized in that** the formulation is produced by build-up and/or break-down granulation, preferably by spray granulation.

5

19. Pharmaceutical formulation according to one of claims 1 to 17, **characterized in that** the formulation is produced by extrusion.

20. Storage stable pharmaceutical formulation comprising at least one
10 active compound in a sustained release matrix,
characterized in that the matrix is a substantially non-swelling diffusion matrix
whose release characteristics are determined by amounts of ethylcellulose or an
ethylcellulose-based polymer and at least one fatty alcohol as matrix components,
and by extrusion or granulation of the matrix materials together with the amount of
15 the active compounds for formation of an active compound-containing matrix.

21. Storage stable pharmaceutical formulation according to claim 20,
wherein the diffusion matrix is a substantially non-erosive matrix.

20 22. Storage stable pharmaceutical formulation according to claim 20 or
21, wherein the matrix material contains ethylcellulose.

23. Storage stable pharmaceutical formulation according to one of claims
20 to 22, wherein the matrix is formed by extrusion, particularly by melt extrusion.

25

24. Storage stable pharmaceutical formulation having an effective amount
of an opioid agonist and/or an opioid antagonist in a substantially non-swelling and
non-erosive diffusion matrix, whose release characteristics are determined by
amounts of ethylcellulose or an ethylcellulose-based polymer and at least one fatty
30 alcohol.

25. Storage stable pharmaceutical formulation according to claim 24
having an effective amount of oxycodone and/or naloxone, with oxycodone being
present in an amount ranging from 10 to 150 mg, preferably from 10 to 80 mg and
5 naloxone being present in an amount ranging from 1 to 50 mg per unit dosage.

26. Storage stable pharmaceutical formulation according to claim 24 or 25
having an effective amount of oxycodone and/or naloxone, wherein oxycodone and
naloxone are present in a weight ratio ranging from maximal 25:1, preferably
10 maximal 20:1, 15:1, particularly preferably 5:1, 4:1, 3:1, 2:1 and 1:1.

27. Method for producing a formulation according to one of claims 1 to
26,
characterized in that granulation, preferably build-up and/or break-down
15 granulation, particularly preferably spray granulation is used.

28. Method of producing a formulation according to one of claims 1 to 26,
being an extrusion method, wherein counter-rotating or co-rotating single or multiple
screw extruders with/without kneading elements are used.
20

29. Method according to claim 28,
being an extrusion method wherein counter-rotating twin-screw extruders, preferably
without kneading elements, are used.

25 30. Method according to claim 28 or 29,
characterized in that the temperature of the heating zones of the extruders is
between 20°-120°C, preferably between 50°-100°C, more preferably between 50°-
90°C and even more preferably between 50°-70°C.

REPLACED BY
ART 34 AMDT

- 64 -

31. Method according to one of claims 28 to 30,
characterized in that the diameter of the nozzle on the extruder is between 1 to 10 mm, preferably between 2 to 8 mm and particularly preferably between 3 to 5 mm.
- 5 32. Method according to one of claims 28 to 31,
characterized in that the resulting temperature in the extruder does not influence the stability of the active compounds.
- 10 33. Method of producing a pharmaceutical dosage form for the treatment of opioid-induced side effects, **characterized in that** the pharmaceutical dosage form comprises a pharmaceutical formulation according to one of claims 1 to 10.
- 15 34. Method according to claim 33, **characterized in that** the preparation is used for treatment of opioid-induced obstipation and preferably for treatment of opioid-induced pruritus.
- 20 35. Method of producing a pharmaceutical dosage form for the treatment of idiopathic syndromes, **characterized in that** the pharmaceutical dosage form comprises a pharmaceutical formulation according to one of claims 1 to 10.
- 25 36. Method according to claim 35, **characterized in that** the preparation is used for treatment irritable bowel syndrome, preferably for treatment of idiopathic pruritus or pruritus due to cholestasia and/or renal dysfunction.

REPLACED BY
ART 34 AMDT

- 65 -

37. Method according to one of claims 33 to 36, **characterized in that** the matrix is a substantially non-swelling diffusion matrix whose release characteristics are determined by amounts of ethylcellulose or an ethylcellulose-based polymer and of at least one fatty alcohol.

5

38. Method according to one of claims 33 to 37, **characterized in that** the preparation comprises between approximately 1 to 50 mg naloxone, preferably between approximately 5 to 30 mg naloxone and even more preferably between approximately 5 to 20 mg naloxone.

10

39. Method according to one of claims 33 to 38, **characterized in that** naloxone is present in the form of its pharmaceutically acceptable and equally active derivatives, such as the free base, salts and the like, preferably as the hydrochloride, sulfate, bisulfate, tartrate, nitrate, citrate, bitartrate, phosphate, malate, maleate,
15 hydrobromide, hydroiodide, fumarate or succinate.

40. Method according to one of claims 33 to 39, **characterized in that** the matrix is produced by extrusion.

20